FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (MODIFIED)	ATTORNEY'S DOCKET NUMBER G-1344
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) 10/031122

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/02361	**06/15/2000 (06.15.00)**	**07/13/1999 (07.13.99)**

TITLE OF INVENTION: SULFONAMIDE SUBSTITUTED BENZYLAMINE DERIVATIVES AND THEIR USE AS MEDICAMENTS

APPLICANT(S) FOR DO/EO/US: Sandra Ginette Milutinovic, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [X] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [X] A copy of the International Preliminary Examination Report (IPER), including any annexes, and, if not in English, an English language translation of the annexes to the IPER under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
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17. [X] The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$750.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee paid to USPTO (37 CRF 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than __20 __30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	27 - 20=	7	**X $18.00**	$ 126.00	
Independent claims	2 - 3=		**X $84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+ $280.00**	$ 280.00	
TOTAL OF ABOVE CALCULATIONS =				$	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 1296.00	
Processing fee of **$130.00** for furnishing English translation later than __ 20 __30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 1296.00	
				Amount to be refunded	$
				charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 05-0840 in the amount of $ 1296.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 05-0840. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
ELI LILLY AND COMPANY
PATENT DIVISION/JAG
LILLY CORPORATE CENTER

Janet A. Gongola
SIGNATURE

Janet A. Gongola
NAME

Date

48,436
REGISTRATION NUMBER

(317) 277-6186
TELEPHONE NUMBER

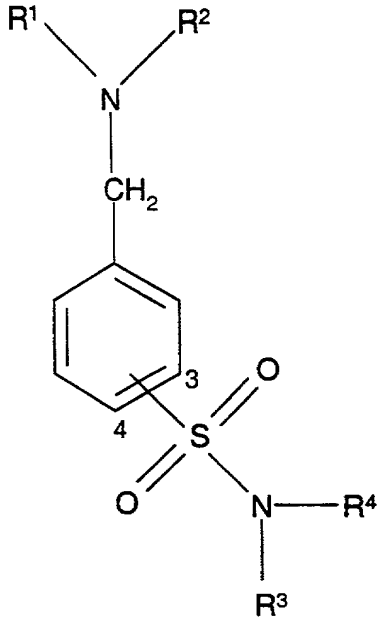
WO 01/04087 PCT/GB00/02361

SULFONAMIDE SUBSTITUTED BENZYLAMINE DERIVATIVES AND THEIR USE AS MEDICAMENTS

This invention relates to novel chemical compounds and their use as pharmaceuticals.

It is well known that chemical compounds which modulate the activity of neuronal calcium channels are potentially useful in treating disorders of the central nervous system.

The compounds of the invention have the following general formula:



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being

optionally fused to an optionally substituted phenyl group;

or a salt thereof.

The compounds of the invention have been found to be active in tests that show modulation of voltage-dependent calcium channels, and are thus indicated for use in the treatment of diseases in which such modulation is beneficial, in particular disorders of the central nervous system.

Thus, the invention includes a method of treating a disorder of the central nervous system, which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder of the central nervous system.

The invention also includes the use of a compound of formula (I), or a pharmaceutically acceptable salt

thereof, in the manufacture of a medicament for treating a disorder of the central nervous system.

In the above formula (I), a C_{1-6} alkyl group includes methyl, ethyl, propyl, isopropyl, butyl, tert. butyl and hexyl, and is preferably methyl or ethyl. A substituted phenyl group is phenyl substituted with one or more, for example one to three, substituents selected from, for example C_{1-4} alkyl, especially methyl, C_{1-4} alkoxy, especially methoxy and ethoxy, hydroxy, nitro, cyano, halo, especially chloro or fluoro, trihalomethyl, especially trifluoromethyl, carboxy and C_{1-4} alkoxy-carbonyl. A halo atom is preferably chlorine, bromine or fluorine. A substituted phenyl group preferably has one to three substituents selected from hydroxy, C_{1-4} alkyl, halo, nitro and trifluoromethyl. An optionally substituted phenyl-C_{1-4} alkyl group is preferably of the formula R-$(CH_2)_n$- where R is optionally substituted phenyl and n is 1 to 4, but the linking chain can also be branched alkylene. A C_{3-10} cycloalkyl group is preferably, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and these groups may optionally be substituted by one or two C_{1-4} alkyl, especially methyl, substituents. A C_{3-10} cycloalkyl-C_{1-4} alkyl group is one such cycloalkyl group attached

to a C_{1-4} alkyl, and is preferably of the formula $R-(CH_2)_n-$ where R is cycloalkyl and n is 1 to 4. When R^3 or R^4 is C_{1-6} alkyl it is preferably C_{3-6} alkyl.

The groups R^1 and R^2, R^3 and R^4, and R^5 and R^6, can form a carbocyclic ring with the nitrogen to which they are attached and optionally also contain an oxygen atom or an additional nitrogen. Preferred examples, including the nitrogen of the amino sulfonyl group, are pyrrolidino, piperazino, morpholino and especially 3,5-dimethylpiperidino.

A particular group of compounds of the invention is one of formula (I) in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1 and R^2, or R^3 and R^4 together with the nitrogen atom to which they are attached, form a carbocyclic group as defined above.

In a preferred group of compounds R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 is in addition hydrogen.

It is preferred that R^1 is hydrogen. Furthermore, R^3 and R^4, which can be the same or different, are preferably C_{1-4} alkyl. It is further preferred that R^2 is optionally substituted phenyl-C_{1-4} alkyl.

A further preferred group of compounds is one of formula (I) in which R^2 is $-(CH_2)_2NR^5R^6$.

A further preferred group of compounds is one of formula (I) in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

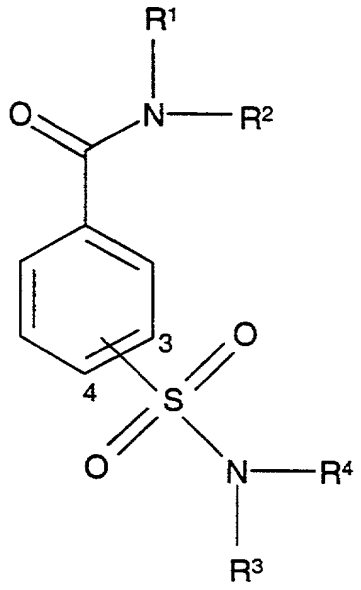
It will be appreciated that the compounds of the invention can contain one or more asymmetric carbon atom which gives rise to enantiomers. The compounds can be prepared as racemates or can be made from enantiomeric intermediates. Both racemates and enantiomers form part of the present invention.

It will also be understood that salts of the compounds of the invention can be prepared and such salts are

included in the invention. They can be any of the well known acid addition salts. Acid addition salts are preferably the pharmaceutically acceptable non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulfuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example glycollic, maleic, fumaric, malic,oxalic, tartaric, citric, salicylic or o-acetoxybenzoic acids, or organic sulfonic acids, methane sulfonic, 2-hydroxyethane sulfonic, toluene-p-sulfonic or naphthalene-2-sulfonic acids.

In addition to pharmaceutically-acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically-acceptable, salts, or are useful for identification, characterisation or purification.

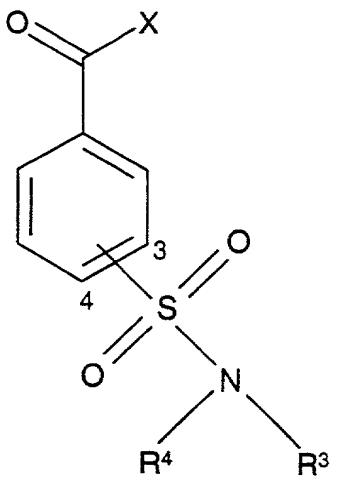
The invention includes a process for producing the compounds of formula (I) above which comprises reducing a compound of the fomula:



(II)

The reaction is preferably carried out in an organic solvent, for example, at a temperature of 0° C. to 100° C., employing a reducing agent, for example lithium aluminium hydride.

Compounds of formula (II) can readily be prepared by conventional methods, for example, by reacting a compound of the formula:



(III)

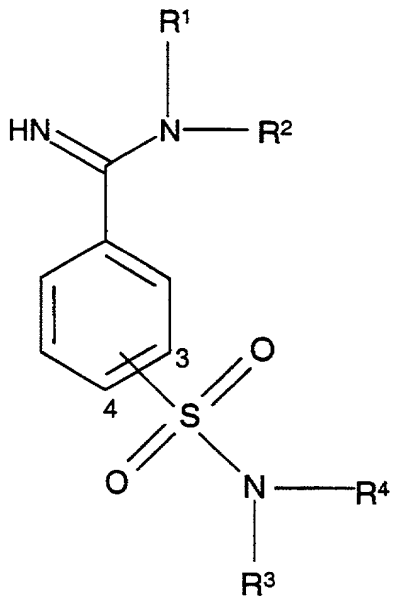
where X is a leaving group such as, for example, halo or hydroxy, with an amine of the formula HNR^1R^2.

The reaction is preferably carried out in an organic solvent such as, for example, chloroform or acetonitrile, at a temperature of from 0° C. to 100° C. such as, for example, ambient temperature.

Intermediate compounds of formula (III) are known in the art and can be readily prepared by known methods. When an acid halide is employed (X is halo such as, for example, chloro), the reaction is preferably carried out in the presence of a solid phase scavenger to absorb the acid liberated by the reaction. When the free acid is employed (X is hydroxy), a condensing reagent such as,

for example, dimethylaminopropyl-ethylcarbodiimide can be employed.

A further route to the compounds of the invention, which is also included in the invention, involves the reduction of the imine corresponding to the compound of formula (III):



(IV)

employing a reducing agent as, for example, sodium borohydride. Compounds of formula (IV) can readily be prepared by reacting an amine of formula R^1R^2NH with the appropriate benzaldehyde derivative, which can, in its turn, be prepared by reducing the corresponding benzoic

acid derivative to the alcohol, followed by oxidation to the required benzaldehyde intermediate.

Amine reactants of the formula HNR^1R^2 are well known and can be readily prepared by known methods. Those in which R^2 is $-(CH_2)_2NR^5R^6$ can, for example, be prepared by reductive amination, that is, by reacting the appropriate diamine with an aldehyde in reducing conditions.

Alternatively, compounds of formula (I) in which R^2 is $-(CH_2)_2NR^5R^6$ can be prepared by alkylation of the corresponding compound of formula (I) in which R^1 is hydrogen.

As mentioned above, the compounds of the invention are active in tests that indicate their utility in the treatment of diseases of the central nervous system. The compounds modulate the activity of calcium channels and, in particular, they block voltage sensitive calcium channels as determined in a test based on Boot J. R., et al., Specificity of autoantibodies in the Lambert-Eaton Myasthenic Syndrome, Ann NY Acad. Sci. (1997), in which measurements of calcium flux using calcium

sensitive dyes are made. Compounds described in the following Examples were found to inhibit voltage-dependent calcium channels in cloned human cell lines expressing specific voltage-dependent calcium channels with an IC_{50} of less than 10 μM.

The compounds of the invention are thus indicated for use in the treatment of anoxia, ischaemia, stroke and heart failure, migraine, diabetes, cognitive impairment, pain, epilepsy, traumatic head or spinal injury, AIDS related dementia and blindness, amnesia, neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases and age-related memory disorders, Down's syndrome, mood disorders, drug or alcohol addition withdrawal, nausea from chemotherapy, and carbon monoxide or cyanide poisoning.

The invention also includes a pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier in association with the compound of the invention or a pharmaceutically acceptable salt or ester thereof.

The compound may be administered by various routes, for example by the oral or rectal route, topically or parenterally, for example by injection or infusion,

being usually employed in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, ointments containing, for example, up to 10% by weight of the compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydrobenzoate, talc magnesium stearate and mineral oil. The compositions of the injection may, as is well known in the art, be formulated so as to provide quick,

sustained or delayed release of the active ingredient after administration to the patient.

Where the compositions are formulated in unit dosage form, it is preferred that each unit dosage form contains from 5 mg to 500 mg. The term 'unit dosage form' refers to physically discrete units suitable as unit dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier.

The active compound is effective over a wide dosage range and, for example, dosages per day will normally fall within the range of from 0.5 to 300 mg/kg, more usually in the range of from 5 to 100 mg/kg. However, it will be understood that the amount administered will be determined by the physician in the light of the relevant circumstances including the conditions to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

The invention is illustrated by the following Preparations and Examples.

EXAMPLE 1

4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid

To a stirred solution of di-n-propylamine (3.03 g, 0.03 mole) in dry tetrahydrofuran (20 ml) at 0° C. (ice/salt bath), was added 4-chlorosulfonylbenzoic acid (2.2 g, 0.01 mole). Stirring was continued for 1 hour. Ice water was added cautiously and the reaction made acid with 2NHCl. The 4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid was collected by filtration as a white solid which was dried *in vacuo* at 40° C.

EXAMPLE 2

4-[(N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide

To a solution of 4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid (2.85 g, 0.01 mole) in dry dichloromethane (ml) at 0° C. was added oxalyl chloride (2.54 g, 0.02 mole) and dimethylformamide (4 drops). The

reaction mixture was stirred for 2 hours. The reaction was evaporated to dryness *in vacuo*. The resulting acid chloride was added to a stirred solution of *p*-methoxybenzylamine (1.51 g, 0.011 mole) and triethylamine (1.11 g, 0.011 mole) in dry tetrahydrofuran (25 ml) at 0-5° C. After stirring for 4 hours the reaction was poured into ice water and extracted with ethyl acetate. The solvent was washed with brine, dried and evaporated to dryness *in vacuo*. Chromatography on flash silica using 10% ethyl acetate/dichloromethane gave 4-{(N,N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide as a white solid. M.p. 132-134° C.

EXAMPLE 3

N,N-di-n-propyl-4-{[(4-methoxybenzyl)amino]methyl} benzenesulfonamide

To a stirred solution of 4-[(N,N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide(1.87g, 4.62mmole) in dry ether (50ml) was added a solution of 2M lithium aluminium hydride in tetrahydrofuran (4.63ml, 9.24mmole). The reaction was heated at reflux for 2 hours. After cooling to room temperature water (1ml)

was added dropwise with caution followed by 2NNaOH (1ml). When gas evolution ceased the reaction mixture was filtered through a pad of celite which was well washed with ether. After removal of the solvent *in-vacuo* the product was purified by chromatography on flash silica eluting with 10% methanol/ethyl acetate. The resulting amine was converted to the maleic acid salt and re-crystallised from ethanol/ether to give *N,N*-di-n-propyl-4-{[(4-methoxybenzyl)amino]methyl} benzenesulfonamide maleate. mp. 133-135°C

Similarly prepared were:

N,N-di-n-propyl-3-{[(4-methoxybenzyl)amino]methyl} benzenesulfonamide maleate. mp. 160-162°C

N,N-di-n-propyl-4-{[(3,4-dimethoxyphenethyl) amino]methyl}benzenesulfonamide maleate. mp. 130-132°C

N-(3,3-dimethylpiperidino)-3-{[(4-fluorobenzyl) amino]methyl}benzenesulfonamide maleate. mp. 169-171°C

N-(3,3-dimethylpiperidino)-4-{[(4-fluorobenzyl) amino]methyl}benzenesulfonamide maleate. mp. 196-198°C

N,N-di-n-propyl-3-{[(4-fluorobenzyl)amino]methyl} benzenesulfonamide maleate. mp. 168-170°C

N-phenyl-*N*-n-propyl-4-{[dimethylamino]methyl} benzenesulfonamide maleate. mp. 154-156°C

N-(3,3-dimethylpiperidino)-3-{[(4-fluorobenzyl)-N-methylamino]methyl}benzenesulfonamide maleate. Mass spectrum:MH^+=405 (TSP+)

N-(3,3-dimethylpiperidino)-3-{[(4-fluorobenzyl)-N-benzylamino]methyl}benzenesulfonamide maleate. mp. 183-185°C

N-phenyl-*N*-methyl-3-{[(4-fluorobenzyl)amino]methyl} benzenesulfonamide maleate. mp. 194-196°C

N-phenyl-*N*-n-butyl-4-{[hexylamino]methyl} benzenesulfonamide maleate. mp. 106-108°C

N-(3-ethylpiperidino)-3-{[(4-fluorobenzyl)amino] methyl}benzenesulfonamide maleate. mp. 140-142°C

N-(3,3-dimethylpiperidino)-3-{[(cyclohexylmethyl) amino}methyl}benzenesulfonamide hydrochloride. mp. 147-149°C

N-(3-methylpiperidino)-4-{[(4-chlorophenethyl)amino] methyl}benzenesulfonamide maleate. mp. 176-178°C

N-(3-methylpiperidino)-4-{[(4-chlorophenethyl)-N-methylamino]methyl}benzenesulfonamide maleate. mp. 168-170°C

3-{[[2-(dimethylamino)ethyl](4-fluorobenzyl) amino]methyl}-*N*-3,3-dimethylpiperidino-benzenesulfonamide maleate as an oil. Mass spectrum(MH^+=462(10%)) (TSP+)

3-{[[2-(dimethylamino)ethyl](cyclohexylmethyl)

amino]methyl}-*N*-3,3-dimethylpiperidino-benzenesulfonamide maleate. mp. 149-151°C

EXAMPLE 4

4-{[[2-(piperidino)ethyl](2-[3,4-dimethoxy]phenylethyl)amino]methyl}-*N*,*N*-di-n-propylbenzene sulfonamide dihydrochloride

To solution of *N*,*N*-di-n-propyl-4-{[(3,4-dimethoxyphenethyl)amino]methyl}benzene sulfonamide(550 mg, 1mmole) in dry acetonitrile (100ml) was added sodium carbonate (440mg, 4.4mmole), potassium iodide (166mg, 1mmole) and 2-chloroethylpiperidine hydrochloride (184mg, 1mmole). The reaction was stirred and heated at reflux for 18 hours. The reaction was poured into ice water and extracted with ethyl acetate, washed with brine, dried and evaporated to dryness *in-vacuo*. Chromatography on flash silica by elution with 10%methanol/dichloromethane gave 4-{[[2-(piperidino)ethyl](2-[3,4-dimethoxy]phenylethyl)amino]methyl}-*N*,*N*-di-n-propylbenzenesulfonamide which was crystallised as its dihydrochloride salt. mp. 135-137°C

EXAMPLE 5

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(4-methylbenzyl)amine

A mixture of a 0.15 M solution of 3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzaldehyde in methanol (0.25 ml) and a 0.1 M solution of 4-methylbenzylamine in methanol (0.25 ml) was stirred at room temperature for 1 hour. A 0.15 M solution of sodium borohydride in methanol (0.25 ml) was added and stirring continued for a further 16 hours. The mixture was then applied to a methanol-washed 500 mg SCX solid phase extraction (SPE) cartridge and washed through with methanol (2.5 ml). The cartridge was then eluted with a 2 M solution of ammonia in methanol (2.5 ml). The eluate was vacuum evaporated to give the required product. (TS-MS: m/z 387, $[M+H]^+$).

The following compounds were similarly prepared (mass spectrum values are given in brackets).

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(4-methylpiperazin-1-yl)propyl]amine (423)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(3-morpholin-4-ylpropyl)amine (410)

N-(4-chlorobenzyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (407/408)

N-(cyclohexylmethyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (379)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(1*H*-imidazol-1-yl)propyl]amine (391)

N-butyl-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (339)

N-(*tert*-butyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (339)

N-(2-chlorobenzyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (407/408)

N-(4-chlorophenethyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (421/422)

N-(2-chlorophenethyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (421/422)

N-(2,4-dichlorobenzyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (442)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-isopentylamine (353)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(3-methoxypropyl)amine (355)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(2-methylbenzyl)amine (387)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(3-methylcyclohexyl)amine (379)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-hexylamine (367)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-propylamine (325)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(4-methylphenethyl)amine (401)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(trifluoromethyl)benzyl]amine (441)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(trifluoromethyl)phenethyl]amine (455)

EXAMPLE 6

1-({3-[(4-benzylpiperidin-1-yl)methyl]phenyl}sulfonyl)-3,3-dimethylpiperidine

A mixture of a 0.15 M solution of 3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzaldehyde in dichloromethane (0.25 ml), a 0.1 M solution of 4-benzylpiperidine in dichloromethane (0.25 ml) and a 0.15 M solution of sodium tri-acetoxyborohydride in dichloromethane (0.25 ml) was stirred at room temperature for 22 hours. Methanol (1 ml) was added and the mixture applied to a methanol-washed 500 mg SCX solid phase extraction (SPE) cartridge and washed through with methanol (2.5 ml). The cartridge was then eluted with a 2 M solution of ammonia in methanol (2.5 ml). The eluate was vacuum evaporated to give the required product. (TS-MS: m/z 441, $[M+H]^+$).

The following compounds were similarly prepared (mass spectrum values are given in brackets).

2-(butyl{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amino)ethan-1-ol (383)

2-(benzyl{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amino)ethan-1-ol (417)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*,*N*-bis(2-methoxyethyl)amine (399)

1-(3,4-dichlorophenyl)-4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazine (497)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-ethyl-*N*-(pyridin-4-ylmethyl)amine (402)

1-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-4-(4-fluorophenyl)piperazine (446)

4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazine-1-carbaldehyde (380)

4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}morpholine (353)

1-[4-(4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazin-1-yl)phenyl]ethan-1-one (470)

3,3-dimethyl-1-{[3-(pyrrolidin-1-ylmethyl)phenyl]sulfonyl}piperidine (337)

2-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-1,2,3,4-tetrahydroisoquinoline (399)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*,*N*-dipropylamine (367)

1-benzhydryl-4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazine (518)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(2-methoxyethyl)-*N*-propylamine (383)

EXAMPLE 7

1-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperidine-4-carboxamide

A mixture of a 0.15 M solution of 3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzaldehyde in methanol (0.25 ml), a 0.1 M solution of piperidine-4-carboxamide in methanol/acetic acid 4:1 v/v (0.25 ml) and a 0.15 M solution of sodium cyanoborohydride in methanol (0.25 ml) was stirred at room temperature for 18 hours. The mixture applied to a methanol-washed 500 mg SCX solid phase extraction (SPE) cartridge and washed through with methanol (2.5 ml). The cartridge was then eluted with a 2 M solution of ammonia in methanol (2.5 ml) and the eluate vacuum evaporated. The residue was dissolved in chloroform (2 ml) and the solution added to isocyanatomethyl-polystyrene (loading 1 mmole/g, 100 mg). The suspension was shaken at room temperature for 16 hours, then filtered. The resin was washed with chloroform (2 x 2 ml) and the combined filtrates vacuum evaporated to give the required product. (TS-MS: m/z 394, $[M+H]^+$).

The following Examples illustrate typical formulations containing a compound of the invention.

EXAMPLE 8

Tablets each containing 10 mg of active ingredient are made up as follows:

Active ingredient	10 mg
Starch	160 mg
Microcrystalline cellulose	100 mg
Polyvinylpyrrolidone (as 10% solution in water)	13 mg
Sodium carboxymethyl starch	14 mg
Magnesium stearate	3 mg
Total	300 mg

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

EXAMPLE 9

Capsules each containing 20 mg of active ingredient are made as follows:

Active ingredient	20 mg
Dried starch	178 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, starch and magnesium stearate are passed through a sieve and filled into hard gelatine capsules in 200 mg quantities.

EXAMPLE 10

Capsules each containing 20 mg of medicament are made as follows:

Active ingredient	20 mg
Lactose	171 mg
Sodium lauryl sulphate	2 mg
Sodium starch glycollate	6 mg
Magnesium stearate	1 mg
	200 mg

The active ingredient, lactose, sodium lauryl sulphate and sodium starch glycollate are mixed thoroughly. The blend is mixed with the magnesium stearate and filled into hard gelatine capsules in 200 mg quantities.

EXAMPLE 11

Tablets each containing 20 mg and medicaments are made as follows:

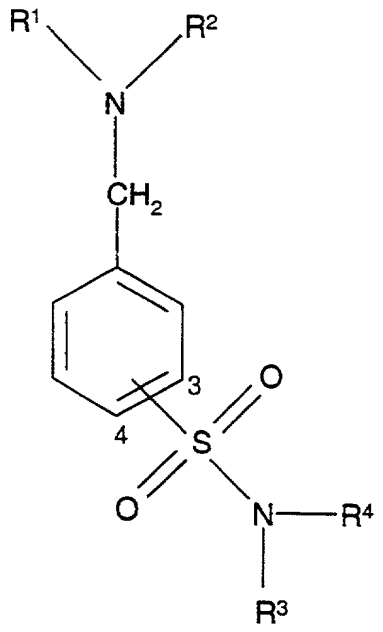
Active ingredient	20 mg
Lactose	103 mg
Microcrystalline cellulose	150 mg
Hydroxypropylmethylcellulose	15 mg
Sodium starch glycollate	9 mg
Magnesium stearate	3 mg
	300 mg

The active ingredient, lactose, microcrystalline cellulose, sodium starch glycollate and hydroxypropylmethylcellulose are passed through a sieve and blended together. Water is added to the blended powders to form a damp mass. The damp mass is passed

through a coarse screen, dried, then re-screened. The dried granules are mixed with the magnesium stearate and compressed into tablets of 300 mg weight.

CLAIMS

1. A compound of the formula



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted

phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group;

or a salt thereof.

2. A compound according to Claim 1 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1 and R^2, or R^3 and R^4 together with

the nitrogen atom to which they are attached, form a carbocyclic group.

3. A compound according to Claim 2 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen.

4. A compound according to Claim 3 in which R^1 is hydrogen, R^2 is optionally substituted phenyl-C_{1-4} alkyl and R^3 and R^4 are C_{1-6} alkyl.

5. A compound according to Claim 1 in which R^2 is $-(CH_2)_2NR^5R^6$.

6. A compound according to Claim 1 or 5 in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

7. A pharmaceutical formulation comprising a compound according to any of Claims 1 to 6 or a pharmaceutically acceptable salt thereof, together with a diluent or carrier therefor.

8. A compound according to any of Claims 1 to 6, for use as a pharmaceutical.

9. Use of a compound according to any of Claims 1 to 6, in the manufacture of a medicament for treating a disorder of the central nervous system.

10. A method of treating a disorder of the central nervous system which comprises administering an effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

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PTO/SB/01 (8-96) (MODIFIED)

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing

[ ] Declaration Submitted after Initial Filing

Attorney Docket Number	**G-1344**
First Named Inventor	**Milutinovic, et al.**
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named Inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole Inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the Invention entitled:

SULFONAMIDE SUBSTITUTED BENZYLAMINE DERIVATIVES AND THEIR USE AS MEDICAMENTS

the specification of which
[ ] is attached hereto
OR
[X] was filed on (MM/DD/YYYY) 06/15/2000 as United States Application Number or PCT International Application Number PCT/GB00/02361 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or Inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached YES	Certified Copy Attached NO
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
9916434.5	07/13/1999

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Attorney Name	Reg. No.
Arvie J. Anderson	45,263
Lynn D. Apelgren	45,341
Robert A. Armitage	27,417
Brian P. Barrett	39,597
Michael T. Bates	34,121
Roger S. Benjamin	27,025
Gary M. Birch	48,881
William R. Boudreaux	35,796
Steven P. Caltrider	36,467
Paul R. Cantrell	36,470
Charles E. Cohen	34,565
Donald L. Corneglio	30,741
Gregory A. Cox	47,504
Paula K. Davis	47,517
Elizabeth A. Dawalt	44,646
John C. Demeter	30,167
Manisha A. Desai	43,585
Joanne Longo Feeney	35,134
Paul J. Gaylo	36,808
Francis O. Ginah	44,712
Janet A. Gongola	48,436
Amy E. Hamilton	33,894
Frederick D. Hunter	26,915
Thomas E. Jackson	33,064
Charles Joyner	30,466
Gerald P. Keleher	43,707

Attorney Name	Reg. No.
James J. Kelley	41,888
Paul J. Koivuniemi	31,533
Robert E. Lee	27,919
Kirby Lee	47,744
James P. Leeds	35,241
Nelsen L. Lentz	38,537
Douglas K. Norman	33,267
Arleen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
Michael J. Sayles	32,295
Robert L. Sharp	45,609
David M. Stemerick	40,187
Mark J. Stewart	43,936
Robert D. Titus	40,206
Robert C. Tucker	45,165
Tina M. Tucker	47,145
MaCharri Vorndran-Jones	36,711
Gilbert T. Voy	43,972
Thomas D. Webster	39,872
Lawrence T. Welch	29,487
Alexander Wilson	45,782
Dan L. Wood	48,613

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	ELI LILLY AND COMPANY						
Address	ATTN: Janet A. Gongola						
Address	LILLY CORPORATE CENTER/DC1104						
City	INDIANAPOLIS	**State**	INDIANA	**ZIP**	46285		
Country	US	**Telephone**	(317) 277-6186	**Fax**	(317) 276-3861		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ **A Petition has been filed for this unsigned inventor**

Given Name	Sandra	Middle Name	Ginette	Family Name	Milutinovic	Suffix e.g. Jr.	

Inventor's Signature		Date	3-DEC-2001

Residence: City	Reading	State	Berkshire	Country	UK GB	Citizenship	FR
Address	39 Devonshire Park,						
Post Office Address	SAME AS ABOVE						
City	Reading	State	Berkshire	Postal Code	RG2 7DX	Country	UK

[X] **Additional Inventors are being named on supplement sheet(s) attached hereto.**

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:													
		☐ A Petition has been filed for this unsigned inventor											
Given Name	Robin	Middle Name	George	Family Name	Simmonds	Suffix e.g. Jr.							
Inventor's Signature	R C Simmonds						Date	3/12/01					
Residence: City	Wokingham	State	Berkshire	Country	UK GB				Citizenship	UK			
Address	2 Plover Close,												
Post Office Address	SAME AS ABOVE												
City	Wokingham	State	Berkshire	Postal Code	RG41 3JD	Country	UK						

Name of Additional Joint Inventor, if any:													
		☐ A Petition has been filed for this unsigned inventor											
Given Name	David	Middle Name	Edward	Family Name	Tupper	Suffix e.g. Jr.							
Inventor's Signature	David Edward Tupper						Date	3/1/02					
Residence: City	Reading	State	Berkshire	Country	UK GB				Citizenship	UK			
Post Office Address	8 Mildenhall Close, Lower Earley,												
Post Office Address	SAME AS ABOVE												
City	Reading	State	Berkshire	Postal Code	RG6 3AT	Country	UK						